REMARKS

Status of the Claims

Claims 46-59 are currently pending.

Claim Amendment

As a general comment, claims 46 and 56 have been amended to remove the reference to "valproate compound". This phrase has been replaced with the phrase "divalproex sodium". Additionally, claims 46 and 56 have been amended to recite "an oral" pharmaceutical composition. Claim 46 has been amended to remove the phrases "to a steady state population of patients, provides an" and "average pharmacokinetic curve such that the plasma concentration levels". The phrases "follows a zero-order release pattern thus producing" and "when determined at a steady state in a healthy fasting population" has been added. Claim 48 has been amended to remove the phrase "average pharmacokinetic maintains a plasma level of". The phrase "plasma levels maintain" has been added. In claim 56, the phrase "to a steady state population of patients" has been deleted. The phrase "when determined at a steady state in a healthy fasting population" has been added. Claims 47, 49, 50, 57 and 59 have been deleted.

Claim Rejections – 35 U.S.C. Section 112

Claims 46-59 are rejected under 35 U.S.C. Section 112, first paragraph, as not being enabling. Specifically, the Examiner argues that the specification is enabling for oral formulations of a specific composition to deliver divalproex sodium, but is not enabling for any pharmaceutical formulation comprising any valproate compounds. Applicants respectfully traverse.

While not agreeing with the Examiner, in order to expedite prosecution, claims 46 and 56 have been amended to recite divalproex sodium. Additionally, claims 46 and 56 have been amended to recite that the pharmaceutical composition is an "oral" composition. Dependent claims 48 and 51-55 refer back to claim 56. In view of this amendment, this rejection is now moot and should be withdrawn.

Claims 46-59 are rejected under 35 U.S.C. Section 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner says that the amended claims add new matter that is not described in the original specification. More specifically, the Examiner says that nowhere have Applicants disclosed: (1) "steady state population"; (2) "essentially flat

average pharmacokinetic curve such that plasma concentration level vary within a range of about 30 μg/ml; and (3) "one or more dosage units collectively containing daily doses". Moreover, the Examiner says Applicant does not describe: (4) "composition provides a mean steady-state AUC_{0-24} measurement of valproate that is at least 80% of the mean steady-state AUC_{0-24} measurement of valproate provided by an enteric-coated delayed-release divalproex sodium tablet given twice a day"; (5) "composition provides a mean steady-state C_{max} of valproate that is statistically significantly lower than the mean steady-state C_{max} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day"; (6) "composition having mean steady-state degree of fluctuation of valproate less than the mean steady-state degree of fluctuation of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day"; (7) "composition having mean steady-state T_{max} of valproate at least twice as long as the mean steady-state T_{max} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day"; and (8) "composition having mean steady-state C_{min} of valproate is not statistically different than the mean steady-state C_{min} of valproate provided by th enteric-coated delayed-release divalproex sodium tablet given twice a day". Applicants respectfully traverse.

With respect to items (1) – (3) discussed above and the new matter rejection, Applicants have amended claims 46 and 46 to address the Examiner's rejection. Moreover, claims 49 and 59 have been deleted.

With respect to items (4)-(8) discussed above, Applicants disagree with the Examiner that Applicants have not described these compositions. As discussed in the *MPEP* Section 2163.04, the inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. Specifically, this section of the *MPEP* states:

> A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Id*

Applicants respectfully submit that the Examiner has not met his burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in Applicants' specification a description of the invention as defined by the claims as currently amended. Applicants submit that the specification provides an adequate written description that is

commensurate with the scope of the claims as currently amended. Specifically, Applicants direct the Examiner's attention to Examples 3 and 4 of the specification (page 32, line 11 – page 39, line 16). These examples demonstrate that the claimed pharmaceutical composition of the present invention provides "a mean steady-state AUC_{0-24} measurement of valproate that is at least 80% of the mean steady-state AUC_{0-24} measurement of valproate provided by an enteric-coated delayed-release divalproex sodium tablet given twice a day" (See Regimen C in Example 3 and Regimens B and D in Example 4 (which are the enteric-coated delayed-release divalproex sodium tablet given twice a day)), "a mean steady-state C_{max} of valproate that is statistically significantly lower than the mean steady-state C_{max} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day" (See Regimen C in Example 3), "a mean steady-state degree of fluctuation of valproate less than the mean steady-state degree of fluctuation of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day" (See Regimen C in Example 3 and Regimens B and D in Example 4), "a mean steady-state T_{max} of valproate at least twice as long as the mean steady-state T_{max} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day" (See Regimen C in Example 3), and a "mean steady-state C_{min} of valproate is not statistically different than the mean steady-state C_{min} of valproate provided by th enteric-coated delayed-release divalproex sodium tablet given twice a day" (See Regimen C in Example 3 and Regimens B and D in Example 4). Thus, based on the above description contained in Applicants' specification, one skilled in the art would clearly recognize a description of the invention as defined by the currently pending claims. In view thereof, this rejection is now moot and should be withdrawn.

Claims 46-59 are rejected under 35 U.S.C. Section 112, second paragraph as being indefinite. Specifically, the Examiner says that the phrases "essentially flat average" and "at least" recited by the claims are relative terms, which renders the claims indefinite. Applicants respectfully traverse.

Applicants submit that just because a claim contains relative terms, does not automatically render a claim indefinite under 35 U.S.C. Section 112, second paragraph. Specifically, Applicants respectfully direct the Examiner's attention to *MPEP* Section 2173.05(b). Specifically, this section of the *MPEP* states:

> The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984).

> Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

As further discussed in this section of the *MPEP*, claims containing the word "essentially" have been found to be definite. With respect to the phrase "essentially flat average" as contained in claim 46, Applicants have amended this claim to now recite the phrase "follows a zero-order release pattern thus producing essentially flat plasma levels". Applicants submit that in view of this amendment to claim 46 that one of ordinary skill in the art would clearly and unequivocally understand what is being claimed in light of the detailed description contained in the specification.

With respect to the phrase "at least" contained in the claims. In the claims, the phrase "at least" is used in connection with "at least 80%" and "at least twice as long". Applicants submit that given the detailed description of the invention provide in the specification and the high level of skill in the art, that one of ordinary skill in the art would clearly and unequivocally understand what is being claimed. In view thereof, this rejection is now considered to be moot and should be withdrawn.

Double Patenting

Claims 46-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over: (1) claims 1-8 of U.S. Patent No. 6,511,678; (2) claims 1-7 of U.S. Patent No. 6,528,090; (3) 1-2 of U.S. Patent No. 6,528,091; (4) claims 1-3 of U.S. Patent No. 6,720,004; (5) 1-17 of U.S. Patent No. 6,713,086; and (6) claims 16 and 19 of copending Application No. 10/770,291.

Applicants which to hold this rejection in abeyance until notification from the Examiner of allowable subject matter. Upon receipt from the Examiner of allowable subject matter, Applicants will file the appropriate terminal disclaimers to obviate the above rejections.

Claim Rejections – 35 U.S.C. Section 102(b)

Claims 46-59 are rejected under 35 U.S.C. Section 102(b) as anticipated by "Epilimchrono: A Multidose, Crossover Comparison of Two Formulations of Valproate in Healthy Volunteers", by Roberts et al. According to the Examiner, Roberts et al. disclosed once a day controlled release formulation to deliver divalproex sodium. Roberts et al. provided a comparison between once a day

formulation and twice daily controlled formulation, either enterically coated or not. Further, the Examiner says that the comparison showed once a day formulation of 1000 mg is almost identical to the enteric coated twice a day formulation AUC (0-24 hr), which reads on the claimed range of at least 80%. The Examiner also says that the reference discloses lower mean C_{max} of once a day formulation than twice a day enteric coated formulation. The Examiner continues by saying that Table 2 of Roberts et al. shows that C_{min} was not significantly different in once a day formulation and twice a day enteric coated formulation. With respect to T_{max}, the Examiner says it was the longest with the once a day formulation than the twice a day enteric coated formulation. With respect to the variation in plasma concentration, this is said to be inherent to the specific formulation. Applicants respectfully traverse.

Roberts et al. disclose the results of an investigation that compared the steady state pharmacokinetics and relative bioequivalence of a mixture of sodium valproate and valproic acid administered twice daily (500 mg Epilim® Chrono b.d.) or once daily (1000 mg Epilim® Chrono o.d.) and an enteric coated tablet containing only sodium valproate administered twice daily (500 mg Epilim® EC b.d) (See page 176). The study concludes that the once-daily Chrono regimen was bioequivalent to the twice-daily EC and Chrono formulations with respect to AUC, that the half-life was more or less identical and that the Cmin and Cmax at steady state for the once-daily Chrono were almost identical to those for the twice-daily EC regimen. Applicants respectfully traverse.

Roberts et al. simply do not disclose a pharmaceutical composition that contains sodium valproate that can be administered once per day. The sodium valproate composition described by Roberts et al. is administered twice daily. In addition, there is absolutely nothing in Roberts et al. that discloses or suggest oral pharmaceutical composition comprising divalproex sodium which when administered once a day to a patient follows a zero-order release pattern thereby producing essentially flat plasma levels that vary within a range of about 30 μg/ml when determined at a steady state in a healthy fasting population. Therefore, because each and every element of the claimed invention is not disclosed by Roberts et al., this rejection is improper and should be withdrawn.

Claims 46-59 are rejected under 35 U.S.C. Section 102(b) as being unpatentable over U.S. Patent No. 4,913,906. According to the Examiner, the '906 patent teaches a composition for the controlled release of salts of valproic acid of the active agent. The Examiner also says that the

controlled release formulation results in sustained action fo the drug with small fluctuation of the plasma level over prolonged period of time (col. 1, lines 59-62). Moreover, the Examiner says that the composition is a once a day oral formulation that delivers the drug for 24 hours and shows about a 97% dissolution rate profile after 24 hours. Also, divalproex sodium is disclosed as one of the salts of valproic acid that is suitable for the formulation of the reference. Finally, the Examiner says that the "pharmacokinetics are inherent for the formulation". Applicants respectfully traverse.

Independent claims 46 and 56 have been amended to recite that the pharmaceutical composition contains divalproex sodium. While the '906 patent mentions divalproex sodium, all of the data provided in the examples is directed to compositions containing sodium valproate and valpromide. No pharmacokinetic data for divalproex sodium is provided. There is absolutely nothing in the '906 patent that discloses or suggest oral pharmaceutical composition comprising divalproex sodium which when administered once a day to a patient follows a zero-order release pattern thereby producing essentially flat plasma levels that vary within a range of about 30 μg/ml when determined at a steady state in a healthy fasting population or an oral composition comprising divalproex sodium which when administered once a day to a patient, provides a mean Cmin of about 48 or higher, when determined at a steady state in a healthy fasting population. Therefore, because each and every element of the claimed invention is not disclosed by the '906 patent, this rejection is improper and should be withdrawn.

REQUEST FOR RECONSIDERATION

Reconsideration and withdrawal of all claim rejections are respectfully requested. Applicants believe that the present application is in condition for allowance. Should the Examiner have any questions or would like to discuss any matters in connection with the present application, the Examiner is invited to contact the undersigned. If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account number 04-2223.

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